REMARKS

Claims 75, 76, 78, 80, 82, 83, 87-106, and 108-112 are pending and stand rejected. The specification at pages 4 and 7, and Claims 75, 78, and 82 have been amended to clarify that R_7 is hydrogen or loweralkyl. Support for this amendment is found in formulas II-V (pages 4-8), throughout the examples, and elsewhere in the application as filed. The specification at pages 3 and 6, and Claims 75, 78, and 82 have been amended to correct a clerical error. Reconsideration and allowance of Claims 75, 76, 78, 80, 82, 83, 87-106, and 108-112 in view of the following remarks is respectfully requested.

Rejection under 35 U.S.C. § 112, First Paragraph

The Examiner has rejected Claims 75, 76, 78, 80, 82, 83, 87-106, and 108-112 under 35 U.S.C. § 112, first paragraph, as failing to comply with the enablement requirement. The Examiner acknowledges that the specification is enabling for a method of inhibiting Raf kinase activity in a human or animal subject suffering from a Ras/mitogen-activated protein kinase signal pathway-mediated cancer disorder selected from the group consisting of melanoma, breast cancer, prostate cancer, lung cancer, pancreatic cancer, thyroid cancer, bladder cancer, colon cancer, liver cancer, myeloid leukemia, and villous colon adenoma, comprising administering to the human or animal subject a composition comprising an amount of a compound of the formula (I). However, in the view of the Examiner, the specification does not reasonably provide enablement for inhibiting Raf kinase activity in a human or animal subject comprising administering a composition comprising **any compound** represented by formula (I). Applicants respectfully disagree for the reasons set forth below.

Guidance of the Specification / Working Examples. According to the Examiner, the specification describes results of an *in vitro* assay wherein 1094 compounds of the invention were tested and shown to have a Raf kinase inhibitory activity at an IC_{50} of less than 50 μM.

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However, the Examiner notes that the claims are directed to compounds wherein R_7 is loweralkyl; only two compounds of the 1094 compounds tested have a loweralkyl in the R_7 position; and the specification does not provide any specific data for those two compounds. It is the Examiner's position that one would need to know the activity profile of the specific compounds tested to understand the scope and breadth of the invention. Applicants respectfully disagree.

Independent Claims 75, 78, and 82, and follow-on dependent Claims 76, 80, 83, 87-106, and 108-112, have been amended to clarify that R_7 is hydrogen or loweralkyl. The scope of the amended claims now encompasses most all of the compounds tested, and the Examiner's remarks regarding the two compounds that have a loweralkyl in the R_7 position are believed to be moot.

Applicants respectfully point out that the compounds tested were shown to have a Raf kinase inhibitory activity at an IC_{50} of less than 5 μM (not 50 μM). (See specification, page 309, lines 14-15.) The specification teaches that a Raf inhibitor is a compound that exhibits an IC_{50} with respect to Raf kinase activity of no more than about 100 μM and more typically not more than about 50 μM. (See specification, page 10, lines 6-8.) All of the compounds tested showed a Raf kinase inhibitory activity at an IC_{50} of less than 5 μM. Therefore, all of the more than one thousand compounds disclosed exhibit significant activity as Raf inhibitors. The fact that approximately one thousand compounds within the scope of the claims show Raf kinase inhibitory activity at an IC_{50} of less than 5 μM provides strong evidence that the claims are enabled throughout the scope of the genus of compounds.

It is also the Examiner's position that there are no working examples comprising administering any compounds of formula (I). Working examples are not required to comply with the enablement requirement. See M.P.E.P § 2164.02. The specification discloses guidance as to methods of administering the compounds of the invention. (See specification, page 28,

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line 14, to page 30, line 10.) Furthermore, 35 U.S.C. § 112, first paragraph, is satisfied if appropriate dosages and methods of administration can be discerned based on information in the art on compounds having similar physiological or biological activity. See M.P.E.P § 2164.01(c). At least one Raf kinase inhibitor (BAY 43-9006) was in clinical trials at the time of filing of the application. Information regarding the BAY 43-9006 trials was published, and therefore guidance as to methods of administration of Raf-kinase inhibitors was provided in the art. See, e.g., Moore, M. et al., "Phase I Study of the Raf-1 Kinase Inhibitor BAY 43-9006 in Patients With Advanced Refractory Solid Tumors," *Proceedings of the American Society of Clinical Oncology 21*: 2002 (abstract 1816); see also, Strumberg, D., et al., "Final Results of a Phase 1 Pharmacokinetic and Pharmacodynamic Study of the Raf Kinase Inhibitor BAY 43-9006 in Patients With Solid Tumors," *Proceedings of the American Society of Clinical Oncology* 21: 2002 (abstract 121). The Moore and Strumberg abstracts are attached as Exhibits A and B, respectively. Since BAY 43-9006 and the compounds of the invention share similar biological activity (inhibition of Raf-kinase activity), and information regarding dosages and administration of BAY 43-9006 were known in the art at the time of filing of the application, then one skilled in the art would be able to discern dosages and methods of administration of the compounds of the invention and 35 U.S.C. § 112, first paragraph, is satisfied.

State of the Art /Predictability of the Art. It is the position of the Examiner that the specification provides no evidence that the compounds of the invention actually inhibit Raf kinase activity in a human or animal. There is no requirement that applicants provide evidence from human clinical trials. See M.P.E.P § 2107.03 (IV). Evidence from *in vitro* testing that shows a compound or compounds exhibit a particular biological activity will be sufficient to show a therapeutic use if the biological activity is reasonably correlated to the therapeutic use. See M.P.E.P § 2107.03 (III). A reasonable correlation can be established by data documenting

the activity of the compound(s), arguments or reasoning, documentary evidence (e.g., articles in scientific journals), or any combination thereof. See M.P.E.P § 2107.03 (I). Evidence of structural similarities between a compound known to have a particular therapeutic use and the claimed compound(s) also may provide support of the asserted therapeutic use of the claimed compound(s). See M.P.E.P § 2107.03 (II).

As discussed supra, more than one thousand compounds of the invention showed Raf kinase inhibitory activity in *in vitro* testing. The compound BAY 43-9006, known as sorafenib, showed Raf kinase inhibitory activity in human trials. See Strumberg, D., et al., supra. Furthermore, BAY 43-9006 and the compounds of the invention share a common structural feature, N-methylpyridine-2-carboxamide. The structure of BAY 43-9006 is attached as Exhibit C. The facts that BAY 43-9006 and the compounds of the invention share a structural feature; BAY 43-9006 has been shown to be an inhibitor of Raf 1 kinase in human clinical trials; and that the compounds of the invention have been shown to be Raf kinase inhibitors in *in vitro* testing, all provide strong support that the compounds of the invention will inhibit Raf kinase activity in a human or animals.

The Examiner also comments on the unpredictability of therapeutic effects, side effects, and serious toxicity that may be generated by drug-drug interactions if compounds of the invention were to be administered with other anticancer agents. It is improper for the Examiner to base his rejections on purported safety issues. See M.P.E.P § 2107.03 (V). It is the responsibility of the FDA, not the Patent Office, to review safety issues. An Examiner must limit review of a patent application to patent law.

The Quantity of Experimentation. It is the position of the Examiner that undue experimentation would be required to practice the claimed invention. Undue experimentation is not determined solely on the basis of the quantity of experimentation or the time and expense

involved. A considerable amount of experimentation is permissible if it is routine. See M.P.E.P. § 2164.06. While drug development is a challenging endeavor, the steps in the process, from *in vitro* testing and animal studies, to the first study in humans, are routine and within the skill of the art.

The Examiner cites *Genentech*, 108 F.3d 1361 (Fed. Cir. 1997) to support his position regarding undue experimentation. In *Genentech*, the claims were directed to a method of producing human growth hormone using cleavable fusion expression. The Federal Circuit held the claims to be invalid for lack of enablement because the specification did not describe in *any* detail how to make human growth hormone using cleavable fusion expression; no reaction conditions were provided; and no description of any specific cleavable conjugate protein was provided. See *Genentech* at 1365. The facts in the present application are not at all analogous to *Genentech*. In contrast to *Genentech*, the present application contains more than just "vague intimations of general ideas." The specification of the present application provides great detail regarding how to make the compounds of the invention. The specification also discloses over one thousand compounds that were made and tested in *in vitro* assays and shown to exhibit Raf kinase inhibition. The Examiner's reliance on *Genentech* is misplaced.

Applicants also point the Examiner to the United States Patent and Trademark Office Training Materials for Examining Patent Applications With Respect to 35 U.S.C. Section 112, First Paragraph - Enablement of Chemical/Biotechnical Applications ("Training Materials") (available at http://www.uspto.gov/web/offices/pac/dapp/1pecba.htm), Example J: Selectin-Mediated Cellular Adhesion. The specification in Example J discloses a genus of compounds and compositions that are useful as inhibitors of P-selectin-mediated cellular adhesion. The specification also describes that the compounds are effective in the treatment of a number of inflammatory diseases, including rheumatoid arthritis, asthma and allergy conditions, and

multiple sclerosis. The specification provides *in vitro* and *in vivo* assays demonstrating that six of the compounds inhibit P-selectin-mediated cellular adhesion, whereas three of the compounds tested did not show inhibitory activity. The specification also provides general guidelines for formulating the compounds in pharmaceutical compositions; dosage amounts and modes of administration. One of the claims is directed to a method for the treatment of diseases characterized by selectin-mediated cellular adhesion, comprising administering a therapeutically effective amount of a compound of claim 1 or a pharmaceutical composition thereof.

According to the Training Materials, the scope of the compounds are enabled because, even though the scope of the claims would encompass compounds that are inactive, the experimentation needed to determine the compounds that show activity and to use those compounds would not be undue.

The present application is analogous to Example J. The specification discloses guidelines as to formulation, dosages, and modes of administration. Whereas Example J only provides test data for nine compounds, three of which are inoperable, applicants have demonstrated that more than one thousand compounds of the genus that were tested show significant activity as Raf kinase inhibitors. Applicants submit that, in view of Example J, the claims are enabled.

Applicants respectfully request withdrawal of the rejection of Claims 75, 76, 78, 80, 82, 83, 87-106, and 108-112 under 35 U.S.C. § 112, first paragraph, because, weighing all the evidence as a whole, the enablement requirement is satisfied.

Rejection under 35 U.S.C. § 112, Second Paragraph

The Examiner has rejected Claims 75, 76, 78, 80, 82, 83, 87-106, and 108-112 under 35 U.S.C. § 112, second paragraph, as being indefinite because the recitations in the claims of "ester or pro-drug thereof" of the compounds of formula (I) are not clearly defined in the specification. The claims have been amended to delete the language "ester or prodrug." The

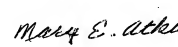
rejection of Claims 75, 76, 78, 80, 82, 83, 87-106, and 108-112 under 35 U.S.C. § 112, second paragraph, is now moot in light of the amendment and applicants respectfully request withdrawal of the rejection.

CONCLUSION

Applicants believe that Claims 75, 76, 78, 80, 82, 83, 87-106, and 108-112 are in condition for allowance. Reconsideration and favorable action is requested. If any issues remain that may be expeditiously addressed in a telephone interview, the Examiner is encouraged to telephone applicants' attorney at 206.695.1795.

Respectfully submitted,

CHRISTENSEN O'CONNOR
JOHNSON KINDNESS^{PLLC}



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Phase I study of the Raf-1 kinase inhibitor BAY 43-9006 in patients with advanced refractory solid tumors.

Sub-category: Molecular/Ligand Targeted Therapies
Category: Biologic and Targeted Therapies
Meeting: 2002 ASCO Annual Meeting

Abstract No: 1816
Citation: Proc Am Soc Clin Oncol 21: 2002 (abstr 1816)

Author(s): Malcolm Moore, Hal Hirte, Amit Oza, Lillian Siu, Sebastien Hotte, Heather Harris, Martha MacLean, Oana Petrenciuc, Wendy Fiander, Chetan Lathia, Princess Margaret Hospital, Toronto, ON, Canada; Hamilton Regional Cancer Centre, Hamilton, ON, Canada; Bayer Inc, Etobicoke, ON, Canada; Bayer Inc, Westhaven, CT.

Abstract: Introduction: Raf-1 is a protein kinase that exerts its effects downstream of Ras in the mitogen-activated proteir kinase pathway and is thus likely to be crucial in the development of a malignant phenotype. BAY 43-9006 is a selective inhibitor of Raf-1 and the first compound of its class to enter clinical trials. The present phase I study was designed to determine the maximal tolerated dose (MTD), toxicity profile, pharmacokinetics and antitumor activity of BAY 43-9006 in patients with refractory solid tumors. Patients and Methods: BAY 43-9006 was administered orally in escalating doses to eligible patients (pts) during the first 28 days of a 35-day cycle. To date, 25 pts have been entered in 6 cohorts (50 mg twice weekly 3, 50 mg every other day 6, 50 mg OD 4, 100 mg OD 4, 100 mg BID 3, 200 mg BID 5). Data are available for pts entered in the first 5 cohorts (n=20). PS 0-2, median age 51 (range, 33-65), 40% male. Primary tumor types: ovary 9, colon 3, pancreas 3, breast 2, other 3. Pharmacokinetic (PK) profiles were obtained during week 1 and week 5 and where possible, tumor biopsies were obtained at baseline and after 4 weeks of treatment. Peripheral blood lymphocytes of treated pts were analyzed by flow cytometry for inhibition of ERK 1/2 phosphorylation. Results: MTD has not yet been reached. Most drug-related adverse events were mild (grade 1-2) and included pruritus/skin rash 10, dyspepsia 7, diarrhea 5, nausea 5, anorexia 4, and fatigue 4. Grade 3 biochemical abnormalities included ALP 4, lymphocytes 3, bilirubin 1, and AST/ALT 3. In cohort 6, one pt had grade 3 fatigue and this cohort has been expanded. The PK analysis from samples drawn on day 1 are shown in the table.[table] Consistent with its long half-life, there was a 1.6-9-fold accumulation in $AUC_{0\text{-}tau}$ from Day 1 to Day 28. Conclusions: At doses up to 200 mg BID daily, BAY 43-9006 remains well tolerated with no evidence of DLT. The 200 mg BID dose is presently being expanded. Consistent with its half-life, BAY 43-9006 accumulates upon multiple dosing.

PK Results

Cohort	No. Pts	Cmax (mg/ml)	$AUC_{0\text{-}tau}$ (hr*mg/L)
1	3	.60+/-.20	8.7+/-2.5
2	6	.66+/-.37	11.0+/-6.6
3	4	.49+/-.24	7.0+/-2.9
4	4	.86+/-.32	10.7+/-4.4
5	3	1.28+/-.19	6.1+/-3.7

Associated Presentation(s):

1. **Phase I study of the Raf-1 kinase inhibitor BAY 43-9006 in patients with advanced refractory solid tumors.**
   No presentation available
   Meeting: 2002 ASCO Annual Meeting
   Publish: Malcolm J. Moore, MD
   Session: (Published Only)

Other Abstracts in this Sub-Category

1. **KIT mutational status predicts clinical response to STI571 in patients with metastatic gastrointestinal stromal tumors (GISTs)**
   Meeting: 2002 ASCO Annual Meeting Abstract No: 6 First Author: Michael C Heinrich
   Category: Biologic and Targeted Therapies - Molecular/Ligand Targeted Therapies
2. **A rationally designed, targeted tumor treatment approach: a phase II study of imatinib mesylate (Gleevec) in patients with life threatening diseases known to be associated with imatinib-sensitive tyrosine kinases**
   Meeting: 2002 ASCO Annual Meeting Abstract No: 7 First Author: Jane Apperley
   Category: Biologic and Targeted Therapies - Molecular/Ligand Targeted Therapies
3. **Phase I/II study of farnesyltransferase inhibitor R115777 (Zarnestra) in patients with myeloproliferative disorders (MPDs): preliminary results**
   Meeting: 2002 ASCO Annual Meeting Abstract No: 14 First Author: Jason Gotlib
   Category: Biologic and Targeted Therapies - Molecular/Ligand Targeted Therapies

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Abstracts by Malcolm Moore

1. **Expectations from treatment and quality of life of patients who are participating in phase 1 studies**
   Meeting: 2002 ASCO Annual Meeting Abstract No: 1439 First Author: Amit M Oza
   Category: Patient Management - Quality-of-Life Management
2. **Phase I study of the Raf-1 kinase inhibitor BAY 43-9006 in patients with advanced refractory solid tumors.**
   Meeting: 2002 ASCO Annual Meeting Abstract No: 1816 First Author: Malcolm Moore
   Category: Biologic and Targeted Therapies - Molecular/Ligand Targeted Therapies
3. **Phase II study of novel taxane BMS-184476 in previously treated patients with advanced adenocarcinoma involving the stomach or gastroesophageal (GE) junction.**
   Meeting: 2002 ASCO Annual Meeting Abstract No: 591 First Author: Michael J Boyer
   Category: Gastrointestinal Cancer - Upper GI Cancer

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Presentations by Malcolm Moore

1. **Erlotinib plus gemcitabine compared to gemcitabine alone in patients with advanced pancreatic cancer. A phase III trial of the National Cancer Institute of Canada Clinical Trials Group [NCIC-CTG]**
   Meeting: 2005 ASCO Annual Meeting
   Presenter: Malcolm Moore, MD
   Session: Plenary Session I (includes David A. Karnofsky Memorial Lecture) (Plenary Presentation)
   

2. **Gastrointestinal Cancer Non-Colorectal Malignancies**
   Meeting: 2000 ASCO Annual Meeting
   Presenter: Malcolm Moore, MD
   Session: Gastrointestinal Cancer Non-Colorectal Malignancies
   

3. **Prostate Cancer**
   Meeting: 2000 ASCO Annual Meeting
   Discussant: Malcolm Moore, MD
   Session: Prostate Cancer
   

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Final results of a phase I pharmacokinetic and pharmacodynamic study of the raf kinase inhibitor BAY 43-9006 in patients with solid tumors

Sub-category: Molecular/Ligand Targeted Therapies
Category: Biologic and Targeted Therapies
Meeting: 2002 ASCO Annual Meeting

Abstract No: 121

Citation: Proc Am Soc Clin Oncol 21: 2002 (abstr 121)

Author(s): Dirk Strumberg, Richard J Bauer, Jan G Moeller, Ralf A Hilger, Heike Richly, Susanne Kredtke, Cordula Beling, Markus Faghih, R. Heinig, David Hedley, Max E Scheulen, Siegfried Seeber, University of Essen, West German Cancer Center, Essen, Germany; Bayer AG, Wuppertal, Germany; Ontario Cancer Institute, Toronto, ON, Canada.

Abstract: Raf-1 is a protein kinase that acts downstream of Ras, and is thus a significant contributor to the malignant phenotype driven by activated Ras signaling. BAY 43-9006 is a novel potent, orally active inhibitor of Raf-1 anc the first compound in this class to enter clinical trials. The primary objectives of the present study are to: define dose limiting toxicities (DLTs) and maximum tolerated dose (MTD), determine the pharmacokinetic (PK) profile and describe evidence of antitumor activity and inhibition of ERK1/2 phosphorylation in treated patients (pts) BAY 43-9006 was started at weekly doses and developed into continuous daily treatment at doses of 100, 200 400 and 800 mg bid. Forty-six advanced stage cancer pts, most heavily pretreated, median age 56, PS 0-2 with refractory malignancies (19 colorectal, 8 hepatocellular, 4 breast, 2 non-small cell lung, and 13 others) receivec BAY 43-9006. DLT was diarrhea CTC 3 in 2/6 pts treated with 800 mg bid/ daily continuously. Other clinica toxicities included rash (CTC 1-2, n=9 at doses =200mg bid /daily), pancreatitis (CTC 3, n=1 at 100 mg bid /daily) and fatigue (CTC 2-3, n=2 at 800 mg bid /daily), but these were not dose limiting. Prolongec stabilization =6 months of previous progressive disease was seen in 7/46 pts (15%) with colorectal carcinoma (ca) (n=4), hepatocellular ca, NSCLC and neuroendocrine ca (n=1). Median duration of stabilizatio n in all study ptswas 5.7 months (range 3.2 to 17.5). One pt with hepatocellular ca attained a partial response after 20 wks o treatment at 400 mg bid. PK profiles (0-12h), obtained at start of treatment and steady state (after day 7), were AUC0-12h,ss = 73 mg*h/L, Cmax = 9.9 mg/L, and tmax = 1.75 h at 400 mg bid. In summary, BAY 43-9006 is a new Raf-1 inhibitor that is generally well-tolerated using continuous oral dosing. Dose limiting diarrhea occurrec at the 800 mg bid/ daily dose level. One pt with hepatocellular ca has attained a partial response. Final results o the study including evidence of inhibition of ERK1/2 phosphorylation will be reported.

Associated Presentation(s):

1. **Final results of a phase I pharmacokinetic and pharmacodynamic study of the raf kinase inhibitor BAY 43-9006 in patients with solid tumors**
   No presentation available
   Meeting: 2002 ASCO Annual Meeting
   Presenter: Dirk Strumberg, MD
   Session: Biologic and Targeted Therapies (General Poster Session)

Other Abstracts in this Sub-Category

1. **KIT mutational status predicts clinical response to STI571 in patients with metastatic gastrointestinal stromal tumors (GISTs)**
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   Category: Biologic and Targeted Therapies - Molecular/Ligand Targeted Therapies
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Meeting: 2002 ASCO Annual Meeting Abstract No: 14 First Author: Jason Gotlib
Category: Biologic and Targeted Therapies - Molecular/Ligand Targeted Therapies

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Abstracts by Dirk Strumberg

1. **Final results of a phase I pharmacokinetic and pharmacodynamic study of the raf kinase inhibitor BAY 43-9006 in patients with solid tumors**

   Meeting: 2002 ASCO Annual Meeting Abstract No: 121 First Author: Dirk Strumberg
   Category: Biologic and Targeted Therapies - Molecular/Ligand Targeted Therapies

2. **Inhibition of ERK phosphorylation and clinical outcome in patients treated with the Raf kinase inhibitor BAY 43-9006**

   Meeting: 2002 ASCO Annual Meeting Abstract No: 1916 First Author: Ralf A Hilger
   Category: Biologic and Targeted Therapies - Molecular/Ligand Targeted Therapies

3. **Pharmacokinetics (PK) of the liposomal encapsulated fraction (Caelyx, Doxil) as well as released doxorubicin after intravenous infusion of pegylated liposomes: PK based evidence for an indirect tumortargeting and a high systemic disposition of the released drug**

   Meeting: 2002 ASCO Annual Meeting Abstract No: 478 First Author: Heike Richly
   Category: Clinical Pharmacology - Pharmacokinetics

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Presentations by Dirk Strumberg

1. **A pharmacokinetic study of S-1 orally administered under fasting and fed conditions with or without a proton pump inhibitor in patients with advanced solid tumors.**

   No presentation available
   Meeting: 2007 Gastrointestinal Cancers Symposium
   Presenter: Dirk Strumberg, MD
   Session: General Poster Session B (Poster Presentation)

2. **Final report of the phase I clinical program of the novel raf kinase inhibitor BAY 43-9006 in patients with refractory solid tumors**

   No presentation available
   Meeting: 2003 ASCO Annual Meeting
   Presenter: Dirk Strumberg, MD
   Session: Developmental Therapeutics - Molecular (General Poster Session)

3. **Final results of a phase I pharmacokinetic and pharmacodynamic study of the raf kinase inhibitor BAY 43-9006 in patients with solid tumors**

   No presentation available
   Meeting: 2002 ASCO Annual Meeting
   Presenter: Dirk Strumberg, MD
   Session: Biologic and Targeted Therapies (General Poster Session)

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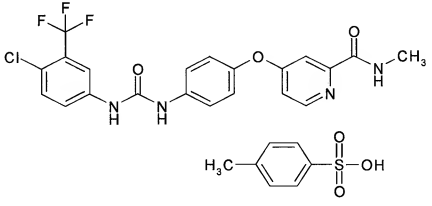
NEXAVAR®

(sorafenib)
tablets 200 mg

DESCRIPTION

NEXAVAR, a multikinase inhibitor targeting several serine/threonine and receptor tyrosine kinases, is the tosylate salt of sorafenib.

Sorafenib tosylate has the chemical name 4-(4-{3-[4-Chloro-3-(trifluoromethyl)phenyl] ureido}phenoxy)-N^2-methylpyridine-2-carboxamide 4-methylbenzenesulfonate and its structural formula is:



Sorafenib tosylate is a white to yellowish or brownish solid with a molecular formula of $C_{21}H_{16}ClF_3N_4O_3$ x $C_7H_8O_3S$ and a molecular weight of 637.0 g/mole. Sorafenib tosylate is practically insoluble in aqueous media, slightly soluble in ethanol and soluble in PEG 400.

Each red, round NEXAVAR film-coated tablet contains sorafenib tosylate (274 mg) equivalent to 200 mg of sorafenib and the following inactive ingredients:

croscarmellose sodium, microcrystalline cellulose, hypromellose, sodium lauryl sulphate, magnesium stearate, polyethylene glycol, titanium dioxide and ferric oxide red.

CLINICAL PHARMACOLOGY

Mechanism of Action

Sorafenib is a multikinase inhibitor that decreases tumor cell proliferation *in vitro*. Sorafenib inhibited tumor growth of the murine renal cell carcinoma, RENCA, and several other human tumor xenografts in athymic mice. A reduction in tumor angiogenesis was seen in some tumor xenograft models. Sorafenib was shown to interact with multiple intracellular (CRAF, BRAF and mutant BRAF) and cell surface kinases (KIT, FLT- 3, VEGFR- 2, VEGFR- 3, and PDGFR- ß). Several of these kinases are thought to be involved in angiogenesis.